



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/55, 31/495, 31/47, 31/445	A1	(11) International Publication Number: WO 99/32125 (43) International Publication Date: 1 July 1999 (01.07.99)
(21) International Application Number: PCT/US98/26223 (22) International Filing Date: 21 December 1998 (21.12.98) (30) Priority Data: 60/068,638 23 December 1997 (23.12.97) US 60/078,638 19 March 1998 (19.03.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 60/078,638 (CIP) Filed on 19 March 1998 (19.03.98) US 60/068,638 (CIP) Filed on 23 December 1997 (23.12.97) (71) Applicant (for all designated States except US): SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): JENSEN, Peder, K. [DK/US]; 40 Gatehouse Road, Bedminster, NJ 07921 (US). LORBER, Richard, R. [US/US]; 9 Michael Lane, Scotch Plains, NJ 07076 (US). DANZIG, Melvyn, R. [US/US]; 8 Lake Louise Road, Morganville, NJ 07751 (US).		MEDEIROS, Paul, T. [US/US]; 248 Taylor Avenue, Easton, PA 18042 (US). (74) Agents: MAJKA, Joseph, T. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: COMPOSITION FOR TREATING RESPIRATORY AND SKIN DISEASES, COMPRISING AT LEAST ONE LEUKOTRIENE ANTAGONIST AND AT LEAST ONE ANTIHISTAMINE		
(57) Abstract <p>A pharmaceutical composition useful in the treatment of sneezing, itching runny nose, nasal congestion, redness of the eye, tearing, itching of the ears or palate, shortness of breath, inflammation of the bronchial mucosa, reduced Forced Expiratory Volume In One Second (FEV₁), coughs, rash, itchy skin, headaches, and aches and pains associated with seasonal allergic rhinitis, perennial allergic rhinitis, common colds, otitis, sinusitis, allergy, asthma, allergic asthma and/or inflammation, in a mammalian organism in need of such treatment. The composition comprises: i) an effective amount of at least one leukotriene antagonist selected from a) montelukast, b) 1-(((R)- (3-(2-(6,7- difluoro-2- quinoliny)ethenyl) phenyl)-3-(2- (2-hydroxy-2- propyl)phenyl) thio)methylcyclopropaneacetic acid; c) 1-(((1(R)-3 (3-(2-(2,3- dichlorothienof[3, 2-b]pyridin-5-yl) -(E)-ethenyl)phenyl) -3-(2-(1-hydroxy-1- methylethyl) phenyl)propyl) thio)methyl) cyclopropaneacetic acid; d) pranlukast; or f) [2-[[2-(4-tert -butyl-2-thiazolyl) -5-benzofuranyl] oxymethyl]phenyl] acetic acid; or a pharmaceutically acceptable salt thereof; in admixture with ii) an effective amount of at least one antihistamine which is descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, astemizole, norastemizole, epinastine, efletirizine or a pharmaceutically acceptable salt thereof.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

COMPOSITION FOR TREATING RESPIRATORY AND SKIN DISEASES, COMPRISING AT LEAST ONE LEUKOTRIENE ANTAGONIST AND AT LEAST ONE ANTIHISTAMINE

5

BACKGROUND OF THE INVENTION

The present invention relates to compositions for treating allergic rhinitis and other allergic diseases. The products of the 5-lipoxygenase pathway of arachidonic acid metabolism, particularly the leukotrienes, can mediate
10 bronchoconstriction, mucous secretion, airway mucosal edema, chemotaxis and mobilization of cells into the airway in the inflammatory process of asthma. Although useful, leukotriene antagonists, in and of themselves, are not capable of effectively treating the multitude of symptoms that may be associated with disease of the respiratory tract, such as season allergic
15 rhinitis, perennial allergic rhinitis, common colds, sinusitis and concomittant symptoms associated with allergic asthma. The symptoms of such diseases may include sneezing, itching runny nose, nasal congestion, redness of the eye, tearing, itching of the ears or palate, and coughs associated with postnasal drip. It would be highly desirable to enhance the
20 efficacy of such leukotriene antagonists to improve their overall efficacy.

SUMMARY OF THE INVENTION

In one embodiment, the present invention is directed towards a pharmaceutical composition comprising:

- 25 i) an effective amount of at least one leukotriene antagonist which is
- a) montelukast,
 - b) 1-(((R)-3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropaneacetic acid;
 - c) 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid;
 - d) pranlukast;
 - e) zafirlukast; or
 - f) [2-[[2-(4-*tert*-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]ac tic
35 acid;

or a pharmaceutically acceptable salt thereof; in admixture with

- ii) an effective amount of at least one antihistamine which is
descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, astemizole,
norastemizole, epinastine, efletirizine or a pharmaceutically acceptable salt
5 thereof.

Preferably the pharmaceutical composition is designed for oral
administration. Preferably the leukotriene antagonist is montelukast and the
pharmaceutically acceptable salt of monoleukast is montelukast sodium.
10 Also preferred is that the pharmaceutically acceptable salt of monoleukast is
about 10 milligrams (mg). Most preferably the antihistamine is
descarboethoxyloratidine. Preferably, a pharmaceutically acceptable salt of
cetirizine or fexofenadine is the hydrochloride salt. Also preferred is that
descarboethoxyloratidine or cetirizine is about 2.5 to about 20 mg, more
15 preferably about 5, 7.5 or 10 mg. Preferably, fexofenadine is from about 60
to 180 mg. More preferably, the pharmaceutically acceptable salt of
monteleukast is about 10 mg and descarboethoxyloratidine is about 5 or 7.5
mg.

Optionally, the pharmaceutical composition can further comprise a
20 third active ingredient which can be:
iii) a decongestant (such as pseudoephedrine), a cough suppressant (such
as dextromethorphan), an expectorant/mucolytic (such as guaifenesin),
NSAIDs or analgesics (such as aspirin, acetaminophen and phenacetin).

The present invention is useful for treating diseases of the skin, the
25 respiratory tract and/or concomittant symptoms associated therewith, in a
mammal, in need of such treatment, comprising administering to said
mammal a pharmaceutical composition as described above. Skin diseases
include atopic dermatitis, psoriasis and chronic idiopathic urticaria,
otherwise known as itchy skin and/or hives. Diseases of the respiratory tract
30 include seasonal allergic rhinitis, perennial allergic rhinitis, common colds,
otitis, sinusitis, allergy, asthma, allergic asthma and/or inflammation.
Symptoms associated with diseases of the respiratory tract include
sneezing, itching and/or runny nose, nasal congestion; redness, tearing or
itching of the eye; itching of the ears or palate, shortness of breath,
35 inflammation of the bronchial mucosa, reduced Forced Expiratory Volume In

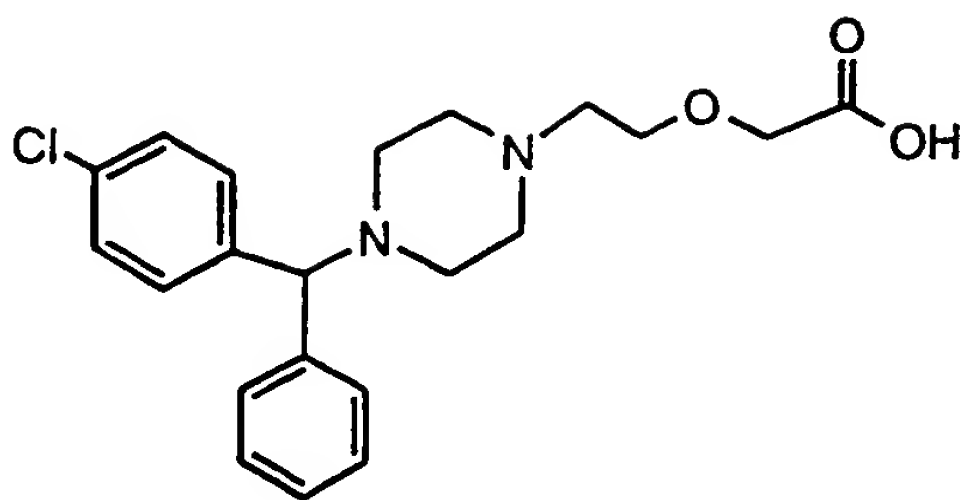
One Second (FEV₁), coughs, rash, hives, itchy skin, headaches, and aches and pains. Descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, astemizole, norastemizole, epinastine, efletirifine or a pharmaceutically acceptable salt thereof and a leukotriene antagonist or pharmaceutically acceptable salt thereof may be administered either either substantially concurrently in separate dosage forms or combined in a unit dosage form as described for the pharmaceutical composition above. Preferably the mammal is a human. Preferably, the separate dosage forms and the unit dosage form of the above pharmaceutical composition are designed for oral administration. Preferably the separate dosage forms and the unit dosage form comprise 5 or 7.5 mg of descarboethoxyloratidine and 10 mg of montelukast sodium.

DETAILED DESCRIPTION OF THE EMBODIMENTS

15 Antihistamines

Descarboethoxyloratidine (DCL) is non-sedating antihistamine, whose technical name is 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2]pyridine. This compound is described in Quercia, et al., Hosp. Formul., 28: 137-53 (1993), in U.S. Patent 4,659,716, and in WO 20 96/20708. DCL is an antagonist of the H-1 histamine receptor protein. The H-1 receptors are those that mediate the response antagonized by conventional antihistamines. H-1 receptors are present, for example, in the ileum, the skin, and the bronchial smooth muscle of man and other mammals. The amount of DCL which can be employed in a unit (i.e. single) 25 dosage form of the present compositions can range from about 2.5 to about 20 mg, also from about 5 to about 10 mg, preferably about 5 or 7.5 mg.

Cetirizine is an antihistamine, whose technical name is (±)-[2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]acetic acid. Preferably the 30 pharmaceutically acceptable salt is the hydrochloride, also known as cetirizine hydrochloride. The chemical structure of this compound is as follows:



The amount of cetirizine which can be employed in a unit dosage form of the present composition can range from about 2.5 to 20 mg, also from about 5 to about 10 milligrams, preferably about 10 milligrams.

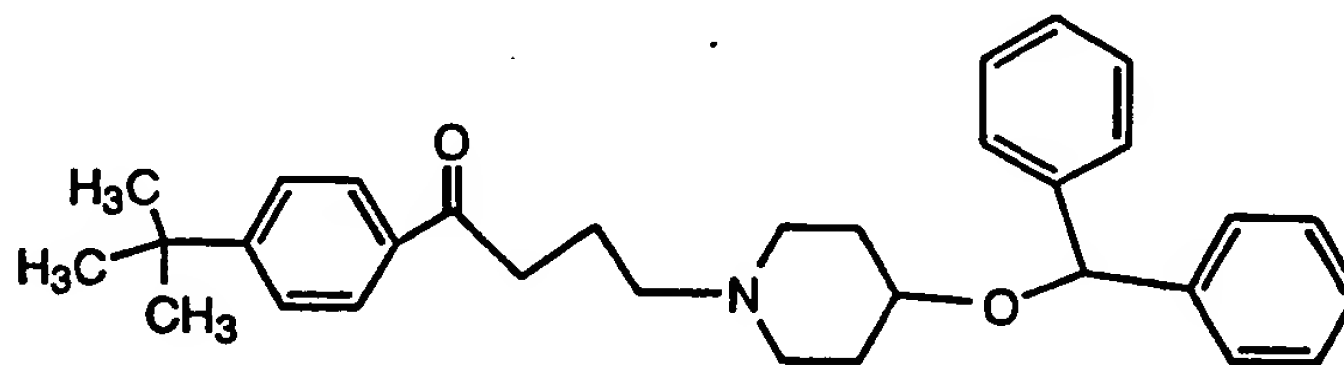
5

Fexofenadine (MDL 16,455A) is a non-sedating antihistamine, whose technical name is 4-[1-hydroxy-4-(4-hydroxy-diphenylmethyl)-1-piperidiny]butyl]- α,α -dimethyl-benzene acetic acid. Preferably the pharmaceutically acceptable salt is the hydrochloride, also known as fexofenadine hydrochloride. The amount of fexofenadine which can be employed in a unit dosage form of the present composition can range from about 40 to 200 mg, also from about 60 to about 180 milligrams, also about 120 milligrams.

10

15

Ebastine is an antihistamine, whose technical name is 1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(diphenylmethoxy)-1-piperidiny]-1-butanone. CAS90729-43-4. The compound is described in EP134124. The chemical structure for this compound is as follows:

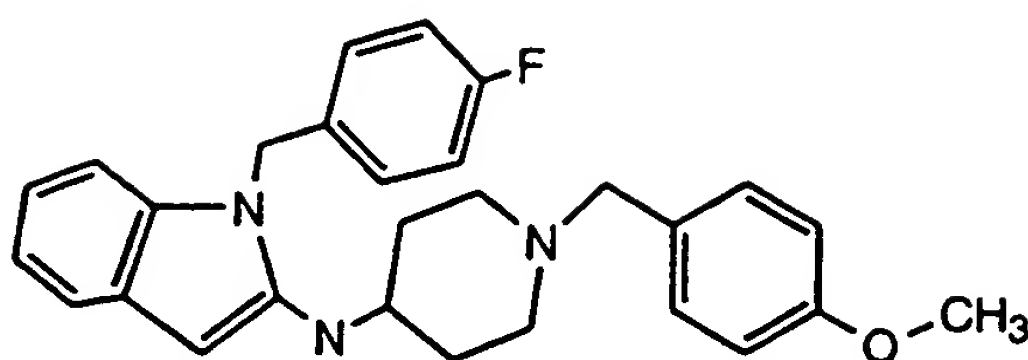


20

The amount of ebastine which can be employed in a unit dosage form can range from about 5 to about 20 mg, preferably about 10 mg.

25

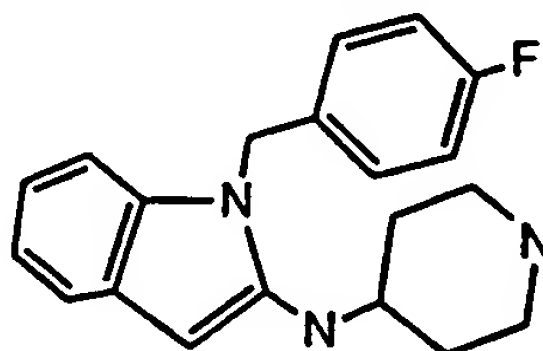
Astemizole is an antihistamine, whose technical name is 1-[(4-fluorophenyl)methyl]-N-[1-[2-(methoxyphenyl)ethyl]-4-piperidiny]-1H-benzimidazol-2-amine. CAS 68844-77-9. The compound is described in US 4,219,559. The chemical structure for this compound is as follows:



The amount of astemizole which can be employed in a unit dosage form can range from about 5 to about 20 mg, preferably about 10 mg.

5

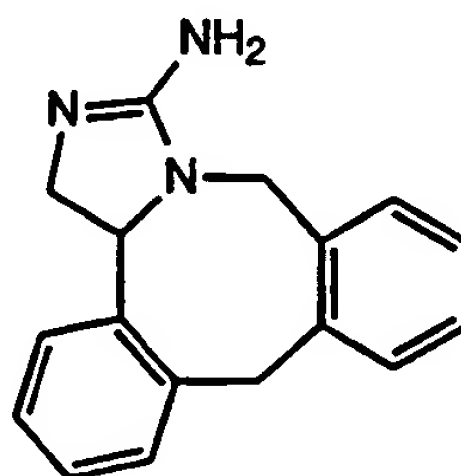
Norastemizole is an antihistamine, whose technical name is 1-((4-fluorophenyl)methyl)-N-4-piperidinyl-1H-benzimidazol-2-amine. CAS 75970-99-9. The compound is an active metabolite of astemizole. The chemical structure for this compound is as follows:



10

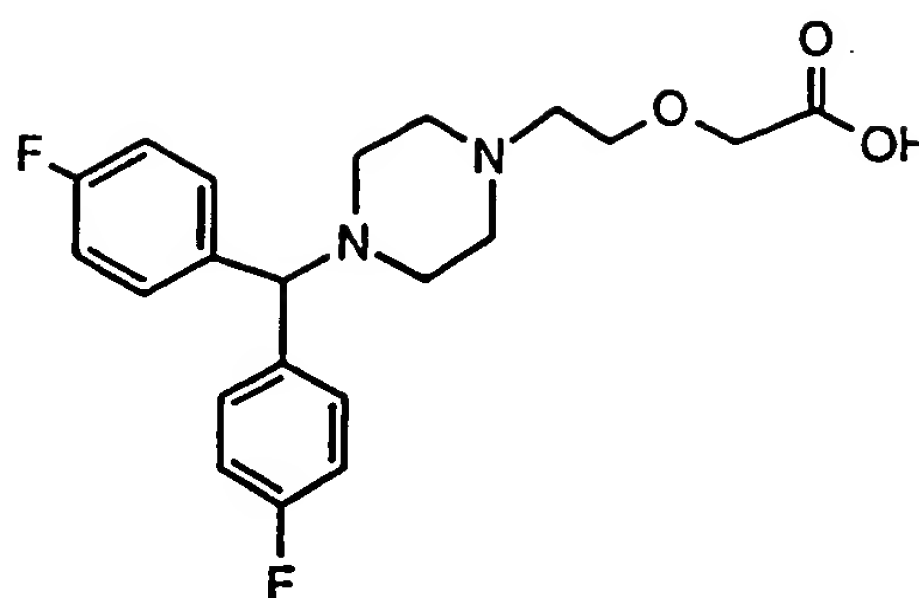
The amount of norastemizole which can be employed in a unit dosage form can range from about 5 to about 40 mg, also from about 10 to about 20 mg.

15 Epinastine is an antihistamine, whose technical name is 9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepin-3-amine. CAS80012-43-7. The compound may be described in DE3008944 or Jpn. J. Clin. Pharmacol Ther, 1991, 22, page 617. The chemical structure for this compound is as follows:



20 The amount of epinastine which can be employed in a unit dosage form can range from about 1 to about 20 mg, preferably about 2 to about 18 mg.

Efletirizine (UCB-28754) is an antihistamine, whose technical name is [2-[4-[Bis(p-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid. CAS140756-35-7. The chemical structure for this compound is as follows:



The amount of efletirizine which can be employed in a unit dosage form can range from about 4 to about 60 mg.

Leukotriene Antagonists

- 5 In addition to and/or in lieu of the amounts cited for any particular compound, the amount of leukotriene antagonist which can be employed in a unit dosage form can range from about 5 to about 500 milligrams, also from about 50 to about 300 milligrams, also from about 100 to about 200 milligrams.
- 10 Montelukast is a leukotriene D4 antagonist capable of antagonizing the receptors for the cysteinyl leukotrienes. The technical name of montelukast is [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid. This compound is described in EP 480,717. A preferred pharmaceutically
- 15 acceptable salt of montelukast is the monosodium salt, also known as montelukast sodium. The amount of montelukast which can be employed in a unit dosage form of the present invention can range from about one to 100 milligrams, also from about 5 to about 20 milligrams, preferably about 10 milligrams.
- 20 The compound 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methyl)cyclopropaneacetic acid is a leukotriene antagonist described in WO 97/28797 and U.S. Patent 5,270,324. A pharmaceutically acceptable salt of this compound is the sodium salt, also known as sodium 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-
- 25 (2-hydroxy-2-propyl)phenyl)thio)methyl)cyclopropaneacetate.

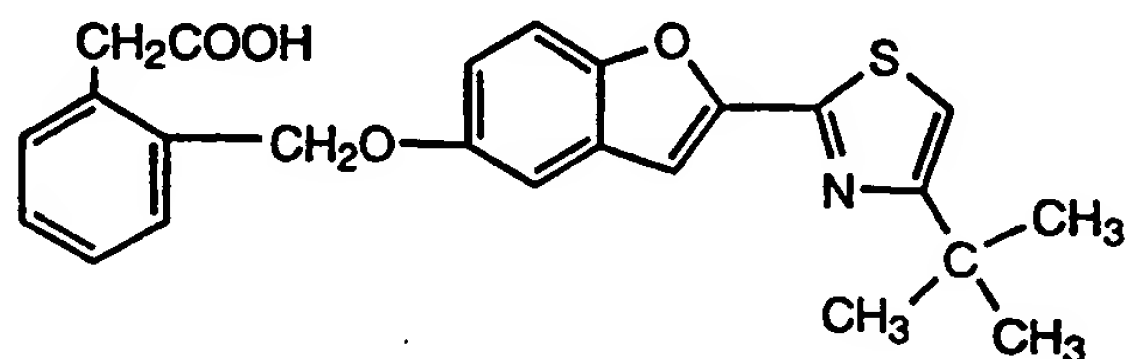
The compound 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-

methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid is a leukotriene antagonist described in WO 97/28797 and U.S. Patent 5,472,964. A pharmaceutically acceptable salt of this compound is the sodium salt, also known as sodium 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetate.

Pranlukast is a leukotriene antagonist described in WO 97/28797 and EP173,516. The technical name for this compound is N-[4-oxo-2-(1H-tetrazol-5-yl)-4H-1-benzopyran-8-yl]-p-(4-phenylbutoxy)benzamide. The amount of pranlukast which can be employed in a unit dosage form can range from about 100 to about 700 mg, preferably from about 112 to about 675 mg; also from about 225 mg to about 450 mg; also from about 225 to about 300 mg.

Zafirlukast is a leukotriene antagonist described in WO 97/28797 and EP 199,543. The technical name for this compound is cyclopentyl-3-[2-methoxy-4-[(o-tolylsulfonyl)carbamoyl]benzyl]-1-methylindole-5-carbamate.

The compound [2-[[2-(4-*tert*-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid is a leukotriene antagonist and/or inhibitor whose method for preparation is described in U.S. Patent 5,296,495 and Japanese patent JP08325265 A. An alternative name for this compound is 2-[[[2-[4-(1,1-dimethylethyl)-2-thiazolyl]-5-benzofuranyl]oxy]methyl]-benzeneacetic acid. The code number for this compound is FK011 or FR150011. The compound has a molecular formula of $C_{24}H_{23}NO_4S$ and molecular weight of 421.52. The chemical structure for this compound is as follows:



The pharmaceutical compositions of the present invention can be administered depending upon the patient's age, sex, weight and severity of the condition being treated. Generally, the human oral dosage form containing descarboethoxyloratidine, cetirizine, fexofenadine, ebastine,

astemizole, norastemizole, epinastine, efletirizine or a pharmaceutically acceptable salt thereof and the leukotriene antagonist can be administered 1 or 2 times per day.

5 The following table sets forth preferred combinations of a leukotriene antagonist and antihistamine.

Leukotriene Antagonist + Antihistamine

Montelukast + Descarboethoxyloratidine

Pranlukast + Descarboethoxyloratidine

Montelukast + Cetirizine

Pranlukast + Cetirizine

Montelukast + Fexofenadine

Pranlukast + Fexofenadine

Montelukast + Ebastine

Pranlukast + Ebastine

Montelukast + Norastemizole

Pranlukast + Norastemizole

Montelukast + Eflightirizine

Pranlukast + Eflightirizine

10 The term "NSAID" as used herein is intended to mean any non-narcotic analgesic non-steroidal anti-inflammatory compound, including the pharmaceutically acceptable salts thereof, falling within one of five structural classes but excluding aspirin, acetaminophen and phenacetin, as follows:

- 1) The propionic acid derivatives such as ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, fenbufen and fluprofen;
- 2) The acetic acid derivatives such as tolmetin sodium sulindac and
15 indomethacin;
- 3) The fenamic acid derivatives such as mefenamic acid and meclofenamate sodium;
- 4) The biphenylcarboxylic acid derivatives such as diflunisal and flufenisal; and
- 20 5) The oxicams such as piroxicam, sudoxicam and isoxicam.

Analgesics are drugs or compounds that relieve pain, including aspirin, acetaminophen and phenacetin.

In the pharmaceutical compositions and methods of the present invention, the foregoing active ingredients will typically be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, syrups, suspensions, solutions, nasal sprays, ophthalmic drops, oral drops, topical creams and the like, and consistent with conventional pharmaceutical practises. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, ie. leukotriene antagonism, antihistaminic and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Dosage form - composition descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, astemizole, norastemizole, epinastine, efletirizine or

a pharmaceutically acceptable salt thereof and leukotriene antagonist formulated into a delivery system, i.e., tablet, capsule, oral gel, powder for constitution or suspension in association with inactive ingredients.

- 5 Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising descarboethoxyloratidine, cetirizine or fexofenadine and leukotriene antagonist. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins.
- 10 The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

- Tablet- refers to a compressed or molded solid dosage form containing the active ingredients (descarboethoxyloratidine, cetirizine or fexofenadine and leukotriene antagonist) with suitable diluents. The tablet
- 15 can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

 Oral gels-refers to descarboethoxyloratidine, cetirizine or fexofenadine and leukotriene antagonist dispersed or solubilized in a hydrophillic semi-solid matrix.

- 20 Powders for constitution refers to powder blends containing descarboethoxyloratidine, cetirizine or fexofenadine and leukotriene antagonist and suitable diluents which can be suspended in water or juices.

- Diluent - refers to to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars
- 25 such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even
- 30 more preferably from about 12 to about 60%.

 Disintegrants - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such

as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binders - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glidents - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

i) an effective amount of at least one leukotriene antagonist selected from

5 a) montelukast,

b) 1-(((R)-3-(2-(6,7-difluoro-2-quinoliny)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropaneacetic acid;

10 c) 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid;

d) pranlukast; or

e) zafirlukast; or

f) [2-[[2-(4-*tert*-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid;

15 or a pharmaceutically acceptable salt thereof; in admixture with

ii) an effective amount of at least one antihistamine which is descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, astemizole, norastemizole, epinastine, efletirizine or a pharmaceutically acceptable salt thereof.

20

2. The pharmaceutical composition of claim 1 wherein the leukotriene antagonist is a) montelukast and the antihistamine is descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, norastemizole or efletirizine.

25

3. The pharmaceutical composition of claim 2 wherein the antihistamine is descarboethoxyloratidine.

30

4. The pharmaceutical composition of claim 2 wherein said montelukast is about 10 milligrams and said descarboethoxyloratidine is about 5 or 7.5 milligrams.

5. The pharmaceutical composition of claim 1 wherein the leukotriene antagonist is d) pranlukast and the antihistamine is descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, norastemizole or efletirizine.
- 5
6. The pharmaceutical composition of claim 5 wherein the antihistamine is descarboethoxyloratidine.
- 10
7. The pharmaceutical composition of claim 1 or 5 further comprising a third active ingredient which can be:
- iii) a decongestant, a cough suppressant, an expectorant/mucolytic or an analgesic.
- 15
8. The pharmaceutical composition of claim 7 wherein the decongestant is pseudoephedrine.
9. The pharmaceutical composition of claim 7 wherein said cough suppressant is dextromethorphan.
- 20
10. The pharmaceutical composition of claim 7 wherein the expectorant/mucolytic is guaifenesin.
- 25
11. A method for treating diseases of the skin, the respiratory tract and/or concomittant symptoms associated therewith, in a mammal, comprising administering to said mammal a pharmaceutical composition of claim 1.
12. Use of the composition of any of claims 1-10 for the manufacture of a medicament useful for treating diseases of the skin, the respiratory tract and/or concomittant symptoms associated therewith in a mammal.

30

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/26223

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/55 A61K31/495 A61K31/47 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	W0 98 34611 A (SEPRACOR INC) 13 August 1998	1, 11, 12
P, A	see page 4, line 28-31; claims 1, 2, 10-13 see page 9, line 30-34	7
P, X	W0 98 48839 A (WARNER LAMBERT CO) 5 November 1998 see page 1-2; claims 1, 4, 8, 9	1, 2, 5, 7, 10-12
X	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 see page 2, line 10-31; claims 1, 5, 6 see page 3, line 27; example 2 see page 4, line 6-8; claims 1, 4-6 see page 4, line 38-40	1, 5, 7, 8, 11, 12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 May 1999

Date of mailing of the international search report

25/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Kanbier, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/26223

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 46243 A (PROCTER & GAMBLE) 11 December 1997 see page 1, line 33 - page 2, line 14 see page 5, line 20-24 see page 5, line 32-34 see page 6, line 15; claims 1,5-10 see page 6, line 17-34 see page 6, line 35 - page 7, line 2 see page 11, line 10-12</p> <p style="text-align: center;">---</p>	<p>1,5,7,8, 11,12</p>
X	<p>EP 0 565 185 A (MERCK FROSST CANADA INC) 13 October 1993 cited in the application see claim 4</p> <p style="text-align: center;">---</p>	<p>1,7,11, 12</p>
A	<p>WO 97 28797 A (S.E. DAHLEN ET AL) 14 August 1997 cited in the application see claims</p> <p style="text-align: center;">---</p>	<p>1,11,12</p>
A	<p>WO 93 03723 A (ALLERGAN INC) 4 March 1993 see page 7-8; claims 1,6,7,12,14 see page 1, line 7-29</p> <p style="text-align: center;">---</p>	<p>1,11,12</p>
A	<p>DE 42 03 201 A (BOEHRINGER INGELHEIM KG) 12 August 1993 see page 6, line 17-20</p> <p style="text-align: center;">-----</p>	<p>1,11,12</p>

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 26223

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-12
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-12
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-10, partly 11, 12

Compositions comprising a leukotriene antagonist selected from compounds (a), (b), (c), (d), (e) and (f) (see claim 1 as filed) and at least one antihistamine which is descarboethoxyloratidine, cetirizine, fexofenadine, ebastine, astemizole, norastemizole, epinastine, efletirizine or salts thereof; their use for the manufacture of a medicament for treating diseases of the respiratory tract and symptoms of these diseases, and methods for treating the above diseases,

2. Claims: Partly 11, 12

Methods for treating diseases of the skin with a composition and use of a composition for the manufacture of a medicament for treating diseases of the skin, said composition comprising a leukotriene antagonist and an antihistamine as described in the previous subject.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .ional Application No

PCT/US 98/26223

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9834611 A	13-08-1998	AU 6434898 A	26-08-1998
WO 9848839 A	05-11-1998	AU 6878098 A	24-11-1998
EP 0780127 A	25-06-1997	NONE	
WO 9746243 A	11-12-1997	AU 3153797 A	05-01-1998
EP 0565185 A	13-10-1993	US 5270324 A	14-12-1993
		AT 168100 T	15-07-1998
		AU 3686393 A	14-10-1993
		BG 99085 A	30-06-1995
		CA 2092896 A	11-10-1993
		WO 9321159 A	28-10-1993
		CN 1080169 A	05-01-1994
		CN 1083052 A	02-03-1994
		CZ 9402463 A	17-01-1996
		DE 69319482 D	13-08-1998
		DE 69319482 T	04-02-1999
		ES 2117691 T	16-08-1998
		FI 944734 A	07-10-1994
		HR 930803 A	31-12-1994
		HU 70399 A	30-10-1995
		JP 2504687 B	05-06-1996
		JP 6025173 A	01-02-1994
		MX 9302033 A	29-07-1994
		NO 943792 A	08-12-1994
		SI 9300188 A	31-12-1993
		ZA 9302533 A	04-11-1993
WO 9728797 A	14-08-1997	AU 2257997 A	28-08-1997
		CA 2245162 A	14-08-1997
		CZ 9802487 A	13-01-1999
		NO 983641 A	07-08-1998
		PL 328074 A	04-01-1999
WO 9303723 A	04-03-1993	US 5276044 A	04-01-1994
		AU 658221 B	06-04-1995
		AU 2427092 A	16-03-1993
		CA 2114945 A	15-02-1993
		EP 0599943 A	08-06-1994
		JP 6510042 T	10-11-1994
DE 4203201 A	12-08-1993	AU 3349793 A	03-09-1993
		CA 2129526 A	06-08-1993
		CZ 9401886 A	15-03-1995
		WO 9316036 A	19-08-1993
		EP 0625138 A	23-11-1994
		EP 0902013 A	17-03-1999
		FI 943618 A	04-08-1994
		HR 930102 A	31-12-1998
		HU 68419 A	28-06-1995
		JP 7503718 T	20-04-1995
		MX 9300630 A	01-09-1993
		NO 942903 A	03-10-1994
		NZ 246593 A	27-07-1997
		PL 173789 B	30-04-1998
		PL 173781 B	30-04-1998

Information on patent family members

PCT/US 98/26223

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4203201	A	SG 44837 A	19-12-1997
		SK 91494 A	08-02-1995
		ZA 9300733 A	06-08-1993
<hr/>			